

What Is Claimed Is:

1. A pharmaceutical composition for moulded capsules comprising Eudragit 4135F present in an amount of about 20 to 90% w/w; a lubricant present in an amount of 0 to about 30% w/w; a dissolution modifying excipient present in an amount of about 2.5 to about 70% w/w, and optionally a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w.
2. The composition according to Claim 1 wherein the Eudragit 4135F is present in an amount of about 50 to 90% w/w.
3. The composition according to Claim 1 which comprises a surfactant which is present in an amount of less than 5% w/w.
4. The composition according to Claim 3 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.
5. The composition according to Claim 4 wherein the surfactant is sodium dodecyl sulphate is present in an amount of less than 2% w/w.
6. The composition according to Claim 4 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.
7. The composition according to Claim 1 wherein the lubricant is present in an amount of about 10 to 30% w/w.
8. The composition according to Claim 1 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof.
9. The composition according to Claim 8 wherein the lubricant is stearyl alcohol.
10. The composition according to Claim 9 wherein the stearyl alcohol is present from about 10 to about 15% w/w.

11. The composition according to Claim 1 wherein the dissolution modifying excipient is a swellable solid which is ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative; and combinations or mixtures thereof.

12. The composition according to Claim 11 wherein the dissolution modifying excipient is hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or hydroxypropyl cellulose.

13. The composition according to Claim 12 wherein the swellable solid is present in an amount of 10 to 50% w/w.

14. The composition according to Claim 1 wherein the dissolution modifying excipient is xylitol, mannitol, lactose, Starch 1500, sodium chloride, sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), copovidone, polyvinyl pyrrolidone copovidone; and combinations or mixtures thereof.

15. The composition according to Claim 14 wherein the dissolution modifying excipient is present in an amount of 40 to 70% w/w.

16. The composition according to Claim 11 wherein the dissolution modifying excipient is a combination of a swellable solid and lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone copovidone.

17. The composition according to Claim 16 wherein the dissolution modifying excipient is hydroxypropylcellulose and lactose.

18. The composition according to Claim 1 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium dodecyl sulphate, Polyoxyl 40 hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid ester; and combinations and mixtures thereof.

19. The composition according Claim 18 wherein the dissolution modifying excipient is a combination of a swellable solid and lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone copovidone.

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20. The composition according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof.

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21. The composition according to Claim 1 wherein the processing agent is talc.

22. The composition according to Claim 21 wherein the processing agent is present in an amount of about 1 to about 5 % w/w.

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23. The composition according to Claim 1 which further comprises an absorption enhancer.

24. The composition according to Claim 23 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS; and combinations or mixtures thereof.

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25. The composition according to Claim 1 wherein the Eudragit 4135F is present in an amount of about 50 to 90% w/w, the lubricant is stearyl alcohol, and the dissolution modifying excipient is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof.

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26. The composition according to Claim 25 wherein the dissolution modifying excipient also includes a disintegrant.

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27. The composition according to Claim 26 wherein the disintegrant is sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone copovidone, or a combination or mixture thereof.

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28. The composition according to Claim 25 wherein the dissolution modifying excipient also includes a wicking agent.
29. The composition according to Claim 28 wherein the wicking agent is lactose.
30. The composition according to Claim 25 wherein the processing aid is talc.
31. The pharmaceutical composition according to Claim 1 which is:

Formulation (%w/w)	
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Croscarmellose sodium	20.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Sodium starch glycollate	20.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Xylitol	10.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Croscarmellose sodium	10.0
Xylitol	10.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Mannitol	10.0
Sodium starch glycollate	10.0
Eudragit 4135F	65.0
Stearyl alcohol	5.0
Mannitol	10.0
Sodium starch glycollate	20.0

Eudragit 4135F	80.0
Stearyl alcohol	5.0
Sodium starch glycollate	10.0
Lactose monohydrate	5.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Sodium starch glycollate	10.0
Lactose monohydrate	10.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Lactose monohydrate	10.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Lactose monohydrate	20.0
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Sodium starch glycollate	5.0
Lactose monohydrate	10.0
Eudragit 4135F	70.0
Stearyl alcohol	5.0
Sodium starch glycollate	5.0
Lactose monohydrate	20.0
Eudragit 4135F	75.0
Stearyl alcohol	10.0
Mannitol	7.5
Sodium starch glycollate	7.5
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Starch 1500	10.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Starch 1500	15.0

Eudragit 4135F	80.0
Stearyl alcohol	5.0
Starch 1500	10.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Kollidon CL	10.0
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Sodium starch glycollate	10.0
Lactose monohydrate	5.0
Eudragit 4135F	75.0
Stearyl alcohol	10.0
Sodium starch glycollate	10.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Sodium chloride	5.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Klucel LF	5.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Hydroxypropylmethyl cellulose	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0
Stearyl alcohol	10.0
Hydroxypropylmethyl cellulose	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0
Stearyl alcohol	10.0
Sodium starch glycollate	5.0
Lactose monohydrate	5.0

Eudragit 4135F	80.0
Stearyl alcohol	10.0
Hypromellose phthallate	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0
Stearyl alcohol	10.0
Low substituted hydroxypropyl cellulose	5.0
Lactose monohydrate	5.0
Eudragit 4135F	90.0
Stearyl alcohol	5.0
Hydroxypropylmethyl cellulose	5.0
Eudragit 4135F	90.0
Stearyl alcohol	5.0
Lactose monohydrate	5.0
Eudragit 4135F	73.0
Stearyl alcohol	12.0
Hydroxypropylmethyl cellulose	10.0
Lactose monohydrate	5.0
Eudragit 4135F	84.0
Sodium dodecyl sulphate	1.0
Croscarmellose sodium	15%
Eudragit 4135F	79.0
Sodium dodecyl sulphate	1.0
Croscarmellose sodium	10%
Sodium starch glycollate	10%
Eudragit 4135F	80.0
Croscarmellose sodium	10%
Sodium starch glycollate	10%
Eudragit 4135F	69.0
Sodium dodecyl sulphate	1.0
Croscarmellose sodium	15%
Sodium starch glycollate	15%
Eudragit 4135F	79.0
Pluronic F68	1.0
Sodium starch glycollate	20%

Eudragit 4135F	79.0
Pluronic F127	1.0
Sodium starch glycollate	20%

32. A pharmaceutical composition for molded capsule shells comprising:

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
4135F	45%	35%	25%	15%	75%	65%	55%
Stearyl Alcohol	10%	10%	10%	10%	10%	10%	10%
Lactose	5%	5%	5%	5%	5%	5%	5%
Klucel LF	40%	50%	60%	70%	10%	20%	30%
Total	100%	100%	100%	100%	100%	100%	100%

33. A pharmaceutical composition for molded capsule shells comprising:

	(1)	(2)	(3)	(4)	(5)	(6)
4135F	63%	62.9%	62.75%	52%	42%	62%
Croscarmellose sodium	10%	10%	10%	15%	20%	5%
Sodium starch glycollate	10%	10%	10%	15%	20%	5%
Stearyl alcohol	12%	12%	12%	12%	12%	12%
Hydroxypropyl-methylcellulose	5%	5%	5%	5%	5%	15%
SDS	0%	0.1%	0.25%	1%	1%	1%.

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34. A pharmaceutical composition for molded capsule shells comprising:

	#(1)	(2)	(3)	(4)	(5)	(6)	(7)
4135F	45%	35%	25%	15%	75%	65%	55%
Stearyl Alcohol	10%	10%	10%	10%	10%	10%	10%
Lactose	5%	5%	5%	5%	5%	5%	5%
Klucel LF	40%	50%	60%	70%	10%	20%	30%
Total	100%	100%	100%	100%	100%	100%	100%

35. A pharmaceutical composition for molded capsule shells comprising:

Formulation	%w/w
Eudragit 4135F	73.0
Hydroxypropylmethyl cellulose	10.0
Lactose (regular)	5.0
Glyceryl monostearate	12.0
Eudragit 4135F	53.0
Hydroxypropylmethyl cellulose	10.0
Lactose (regular)	5.0
Hydroxypropylmethyl cellulose phthallate	20.0
Stearyl alcohol	12.0
Eudragit 4135F	20.0
Hydroxypropylmethyl cellulose	10.0
Hydroxypropylmethyl cellulose phthallate	20.0
Stearyl alcohol	12.0
Eudragit 4135F	68.0
Hydroxypropylmethyl cellulose	10.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	5.0
Stearyl alcohol	12.0
Eudragit 4135F	72.0
Hydroxypropylmethyl cellulose	10.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	71.0
Hydroxypropylmethyl cellulose	10.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	2.0
Stearyl alcohol	12.0
Eudragit 4135F	62.0
Sodium starch glycollate	20.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0

Eudragit 4135F	62.0
Sodium starch glycollate	20.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	72.0
Sodium starch glycollate	10.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	62.0
Croscarmellose sodium	20.0
Lactose (regular)	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	62.0
Sodium starch glycollate	20.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	62.0
Hydroxypropylmethyl cellulose phthallate	20.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	62.5
Sodium starch glycollate	20.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	0.5
Stearyl alcohol	12.0
Eudragit 4135F	62.0
Croscarmellose sodium	10.0
Sodium starch glycollate	10.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0

Stearyl alcohol	12.0
Eudragit 4135F	67.0
Croscarmellose sodium	15.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	72.0
Croscarmellose sodium	10.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	77.0
Croscarmellose sodium	5.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	52.0
Croscarmellose sodium	15.0
Sodium starch glycollate	15.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	42.0
Croscarmellose sodium	20.0
Sodium starch glycollate	20.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	42.0
Croscarmellose sodium	20.0
Sodium starch glycollate	20.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0

Eudragit 4135F	62.0
Croscarmellose sodium	5.0
Sodium starch glycollate	5.0
Hydroxypropylmethyl cellulose	15.0
Sodium dodecyl sulphate	1.0
Stearyl alcohol	12.0
Eudragit 4135F	62.9
Croscarmellose sodium	10.0
Sodium starch glycollate	10.0
Hydroxypropylmethyl cellulose	5.0
Sodium dodecyl sulphate	0.1
Stearyl alcohol	12.0

36. The composition according to Claim 1 wherein

	<u>Dissolution modifier (%)</u>	<u>Lubricant (%)</u>	<u>Surfactant (%)</u>
5 a)	Pharmacoat 603 (5%)	Stearyl alcohol (12%)	none;
b)	Pharmacoat 603 (10%) HPMCphthalate (20%)	Stearyl alcohol (12%)	none;
c)	Pharmacoat 603 (10%) Lactose (5%)	Stearyl alcohol (12%)	none;
10 d)	Pharmacoat 603 (5%) Explotab (20%)	Stearyl alcohol (12%)	SDS (1%) or Tween or Pluronic.

37. The composition according to Claim 1 which is

77% 4135F + 1% SDS + 5% Ac-Di-Sol + 12 % stearyl alcohol (SA) + HPMC 5%
68% 4135F + 15% Ac-Di-Sol + 12 % SA + HPMC 5%
62% 4135F + 1% SDS + 10% Ac-Di-Sol + 10% Explotab + 12 % SA + HPMC 5%
63% 4135F + 10% Ac-Di-Sol + 10% Explotab + 12% SA + HPMC 5%
52% 4135F + 1% SDS + 15% Ac-Di-Sol + 15% Explotab + 12 % SA + HPMC 5%

62% 4135F + 1% Pluronic F68 + 20% Explotab + 12 % SA + HPMC 5%
62% 4135F + 1% Pluronic F127 + 20% Explotab + 12 % SA + HPMC 5%
Eudragit 4135F 62% + Stearyl Alcohol (SA) 12% + AcDiSol 5%, Explotab 5% + HPMC 15% + SDS 1%
Eudragit 4135F 42% + SA 12% + AcDiSol 20% + Explotab 20% + HPMC 5% + SDS 1%
Eudragit 4135F 47% + SA 12% + Explotab 10% + HPMC 30% + SDS 1%

38. The composition according to Claim 1 wherein the lubricant is stearyl alcohol present in an amount of 10 to 15% w/w, the lubricant is SDS or a present in an amount of a block copolymer of ethylene oxide and propylene oxide at less than 5% w/w; a dissolution modifying excipient is HPC, HPMC, sodium starch glycollate, croscarmellose sodium, copovidone, or lactose, and combinations or mixtures thereof, present in an amount of about 2.5 to about 70% w/w.

39. An injection molded capsule shell, linker or spacer having a composition according to Claim 1.

40. A multicomponent injection molded capsule shell, linker or spacer having a composition according to Claim 1.

41. A welded multicomponent injection molded capsule shell, linker or spacer having a composition according to Claim 1.

42. A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

a) a drug substance-containing capsule compartment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment, and

b) a solid matrix comprising a polymer and containing a drug substance, the polymer being soluble, dispersible or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the solid matrix, and in which, at least prior to administration to a patient, the sub-units are welded together

in an assembled dosage form.

43. A multi-component pharmaceutical dosage form according to Claim 42, in which at least one of the sub-units is a solid matrix comprising Eudragit 4135F present in an amount of about 20 to 90% w/w, and a dissolution-modifying excipient present in an amount of about 2.5 to about 30% w/w.

44. A multi-component pharmaceutical dosage form according to Claim 43, in which the solid matrix also comprises a lubricant present in an amount up to about 30% w/w.

45. A multi-component pharmaceutical dosage form according to Claim 43, in which the solid matrix also comprises a plasticizer present in an amount up to about 10% w/w.

46. A multi-component pharmaceutical dosage form according to Claim 43 in which the solid matrix also comprises a processing agent present in an amount up to about 10% w/w.

47. A dosage form according to Claim 42, comprising plurality of drug substance-containing capsule compartments, each compartment being physically separated from at least one adjacent compartment by a wall made of a pharmaceutically acceptable polymer material.

48. A multi-component pharmaceutical dosage form according to Claim 47, in which the wall comprises Eudragit 4135F present in an amount of about 20 to 90% w/w, and a dissolution-modifying excipient present in an amount of about 2.5 to about 30% w/w.

49. A multi-component pharmaceutical dosage form according to Claim 47, in which the wall also comprises a lubricant present in an amount up to about 30% w/w.

50. A multi-component pharmaceutical dosage form according to Claim 47, in which the wall also comprises a plasticizer present in an amount up to about 10% w/w.

51. A multi-component pharmaceutical dosage form according to Claim 47, in which the wall also comprises a processing agent present in an amount up to about 10% w/w.

5 52. A dosage form according to Claim 47, in which at least one of the sub-units is a drug substance-containing capsule compartments having a wall with a thickness in the range of about 0.3 – 0.8 mm.

53. A dosage form according to Claim 42, in which at least one of the sub-units
10 is a substantially immediate release sub-unit.

54. A dosage form according to Claim 42 which at least one of the sub-units is a sustained release or pulsed release sub-unit.

15 55. A set of multi-component dosage forms, each comprising a plurality of sub-units each sub-unit being selected from:

a) a drug substance-containing capsule compartment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment, and

20 b) a solid matrix comprising a polymer and containing a drug substance, the polymer being soluble, dispersible or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the solid matrix, in which at least one of the dosage forms of the set comprises at least one said drug substance-containing capsule compartment and at least one other dosage form of the
25 set comprises at least one said solid matrix, and in which the drug substance-containing capsule compartment of said at least one of the dosage forms is interchangeable with said solid matrix of said at least one other dosage form, and

30 in which at least prior to administration to a patient, the sub-units of each dosage form are welded together to provide an assembled dosage form.

56. A process for making a pharmaceutical dosage form comprising the steps of:

a) introducing Eudragit 4135F and an excipient composition simultaneously, and at substantially the same location, into an elongated hot melt extruder;

35 b) mixing said Eudragit 4135F and said excipient composition in the hot melt extruder to form a homogeneous composition therein and ejecting the homogeneous composition in the form of a strand from the hot melt extruder though

a die at a location remote from said same location at which the Eudragit 4135F and said excipient composition are introduced;

- c) cutting the strand into pellets;
- d) introducing said pellets into an injection molder and forming thin-walled capsule compartments from said pellets by injection molding.

57. The process according to Claim 56, in which the excipient composition comprises a dissolution modifying excipient.

58. The process according to Claim 56, in which the excipient composition comprises a surfactant.

59. The process according to Claim 56, in which the excipient composition comprises a lubricant.

60. The process according to Claim 56, in which the hot melt extruder is maintained at a temperature not exceeding approximately 135°C.

61. The process according to Claim 56, in which the hot melt extruder is maintained at a temperature not lower than the Eudragit 4135F and said excipient composition melting points.

62. The process according to Claim 56, in which the temperature in the hot melt extruder gradually increases along the length of the hot melt extruder, from said same location at which the Eudragit 4135F and an excipient composition are introduced, to the die, the maximum temperature not exceeding approximately 135°C.

63. The process according to Claim 56, in which the hot melt extruder comprises an elongated barrel having first and second opposite ends, and twin screws within the barrel for propelling Eudragit 4135F and said excipient composition along the length of the interior of the barrel, said substantially same location at which the Eudragit 4135F and said excipient composition are introduced is located adjacent the first end of the barrel, and said die is located adjacent the second end of the barrel.

64. The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a

barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 120°C to 140°C.

65. The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature in the range of about 140°C to 190°C.

66. The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature of about 165 to 170°C.

67. The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 120°C to 140°C and maintaining the injection molder nozzle at a temperature in the range of about 140°C to 190°C.

68. The process according to Claim 56 wherein the pharmaceutical dosage forms are assembled using said capsule compartments as components of said dosage forms.

69. The process according to Claim 68 wherein the said capsule compartments of the assembled dosage form are connected together by at least one weld where adjacent parts of said components are in contact.

70. The process according to Claim 69 wherein the weld is produced by a thermal weld, an ultrasonic weld, an inductive weld, or an adhesive weld.